Healthcare professional Guide
Gedeon Richter Levonorgestrel (LNG) containing intrauterine delivery system (IUS)

This information sheet on Gedeon Richter Levonorgestrel IUS (LNG-IUS) is part of the regulatory requirements to minimise the risk of application errors due to confusion of different types of IUS and to reduce the risk of ectopic pregnancies. It is a mandatory part of the approval and ensures that healthcare professionals who prescribe and use Gedeon Richter LNG-IUS, as well as patients, are aware of the special safety requirements and act accordingly.

Overview

The following Gedeon Richter IUS have been authorised in the United Kingdom:

- Benilexa One Handed, 52mg levonorgestrel (LNG)
- Benilexa, 52mg levonorgestrel (LNG) – not marketed
- Levosert, 52mg levonorgestrel (LNG)

Sections

1. Differentiation of Gedeon Richter LNG-IUS
    a. Duration and indication of application
    b. Pharmaceutical form and release rate
    c. Physical appearance
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2. Risk of ectopic pregnancy

Before inserting a Gedeon Richter LNG-IUS, the patient information leaflet in the package should be given to the woman for her to read.

Section 1. Differentiation of Gedeon Richter LNG-IUS

To differentiate Gedeon Richter LNG-IUS from other levonorgestrel containing IUS by other manufacturers, please read the valid Summaries of Product Characteristics of concerned products.

a. Indication for use and approved treatment duration:

- Benilexa One Handed, and Levosert, are licensed in the indications of:
  - Contraception for up to 8 years.
  - Treatment of heavy menstrual bleeding for up to 3 years. Benilexa One Handed and Levosert may be particularly useful in women with heavy menstrual bleeding requiring (reversible) contraception. The system should be removed or replaced in the event that symptoms return. If symptoms have not returned after 3 years of use, continued used of the system may be considered. Benilexa One Handed and Levosert should be removed or replaced after a maximum 8 years of use.

Please note that different IUS' marketed by different companies may have different indications and may be used for different durations.

Gedeon Richter LNG-IUSs are available with 2 insertion techniques: Benilexa One Handed, with single- handed inserter, and Levosert, with two-handed inserter. The two products differ in the inserter only, the T-body is the same in both. The single-handed and two-handed inserter products are distinguished by their brand names as well. Compared to other LNG-IUS, the Gedeon Richter LNG-IUSs can be distinguished by the absence of a silver ring on the T-body, their blue removal threads and their inserterprofiles.

b. Pharmaceutical form and release rate

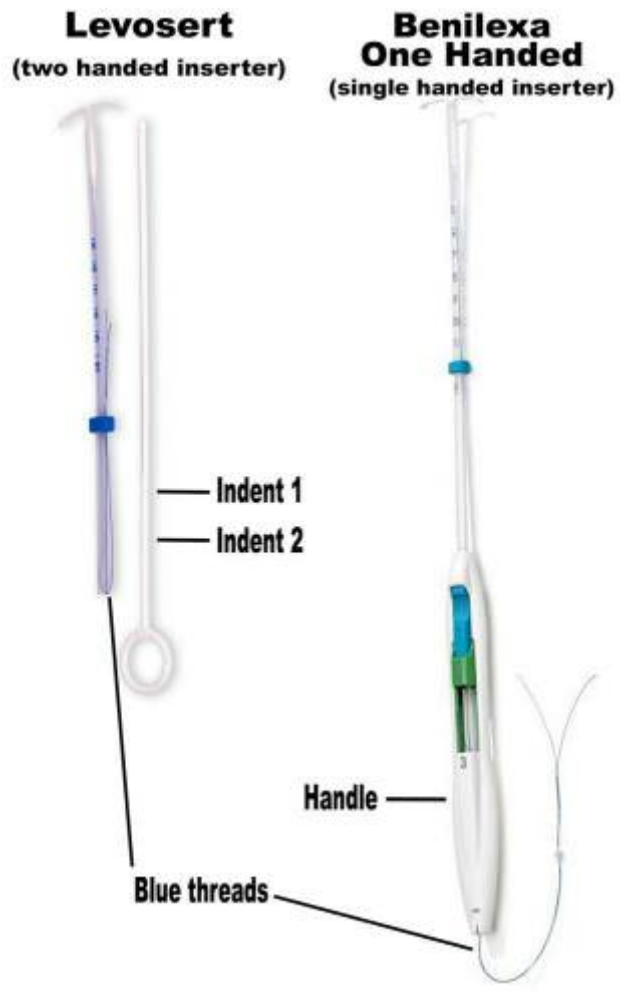
The Gedeon Richter LNG-IUSs are T-shaped, flexible plastic devices which are inserted into the uterine cavity and continuously release levonorgestrel (LNG). The total LNG content, maximum duration of use, appearance and the average in vivo LNG release rates for the products are summarised in Table 1.

Table 1. Main characteristics of Gedeon Richter LNG-IUS

	Benilexa One Handed	Levosert
Total LNG content in mg	52	52
Max. duration of application in years	8	8
Size T-body in mm	32 x 32	32 x 32
Diameter of the insertion tube in mm	4.8	4.8
Silver ring for easier detection in ultrasound	no	no
Colour of the removal threads	blue	blue
Initial release in µg/24 h	20.1	20.1
Release rate after 1 year in µg/24 h	17.5	17.5
Release rate at the end of the indicated application period in µg/24 h	8.6	8.6
Insertion technique	Single handed	Two handed
Inserter indents	No indent	Two indents

c. Physical appearance

Figures 1 includes images of Levosert and Benilexa inserters, while figure 2 indicates the dimensions of the T-body reservoir and the colour of the removal threads.



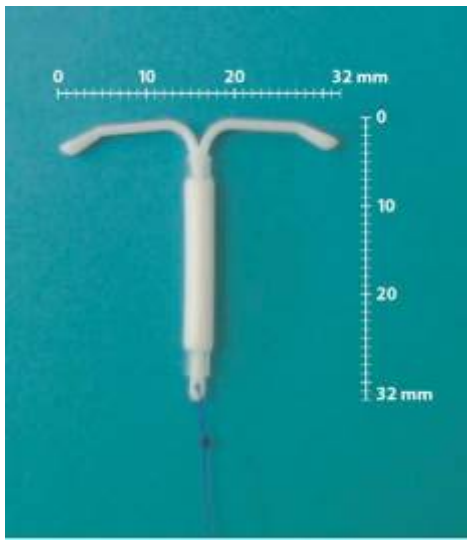


Figure 2: T-body reservoir of Gedeon Richter LNG-IUS with scale and thread colours

d. X-ray and ultrasound appearance

The T-body of Gedeon Richter LNG-IUS contains the X-ray contrast medium barium sulphate and is therefore visible in the X-ray image. Ultrasound appearance is demonstrated in Figure 3 in 2 D and Figure 4 in 3D.

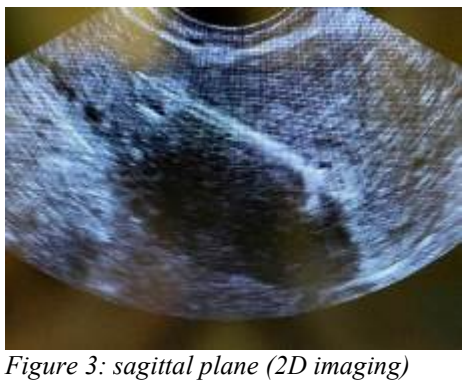


Figure 3: sagittal plane (2D imaging)

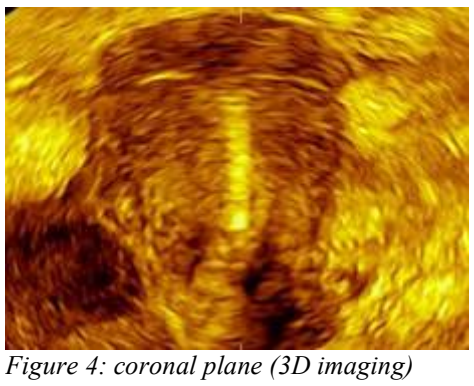


Figure 4: coronal plane (3D imaging)

Conditions for use

The single-handed and two-handed inserter products require different insertion techniques.

Please carefully read the Summary of Product Characteristic/Package Leaflet for detailed insertion instructions. Please also make sure to complete the Patient Reminder Card after inserting Benilexa One Handed or Levosert and give to the patient as a reminder.

Part 2. The risk of ectopic pregnancy with use of LNG-IUS

Since the product information leaflet contains ample information on the risk of ectopic pregnancy, the inserting healthcare professionals are advised to provide the leaflet to the patient before insertion of LNG-IUS.

Background incidence of ectopic pregnancy

In the UK, the incidence of ectopic pregnancy is approximately 11/1000 pregnancies, with an estimated 11000 ectopic pregnancies diagnosed each year.[1]

Ectopic pregnancy in women using LNG-IUS

In users of intrauterine contraception (IUC) the absolute risk of ectopic pregnancy is reduced because they are such effective methods of contraception overall. The absolute risk of ectopic pregnancy is lower than among women not using any contraception. While the absolute risk of ectopic pregnancy is not increased by use of IUC, should a pregnancy occur with an intrauterine method in situ, the likelihood of it being ectopic is greater than if a pregnancy were to occur with no IUC in situ. The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain - especially in connection with missed periods or if an amenorrhoeic woman starts to experience bleeding.

In the conducted clinical study, the overall incidence of ectopic pregnancy with LNG-IUS was approximately 0.12 per 100 woman-years.[2] Women considering LNG-IUS should be counselled on the signs, symptoms and risks of ectopic pregnancy, as described below. For women who become pregnant while using LNG-IUS, the possibility of an ectopic pregnancy must be considered and evaluated.

The risk of ectopic pregnancy in women who have a history of ectopic pregnancy and use LNG-IUS is unknown.

Signs and symptoms of ectopic pregnancy

The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain, especially in connection with missed periods or if an amenorrheic woman starts bleeding. It is important that the signs and symptoms of ectopic pregnancy are detected as early as possible so that treatment can be initiated immediately. It is therefore crucial to educate women about the signs and symptoms of ectopic pregnancy, including the following[3,4,5] :

- Unilateral abdominal pain, which can be severe or persistent. The pain can occur suddenly and abruptly or increase slowly over several days.
- Vaginal bleeding. This may differ from menstrual bleeding (e.g. the blood may be darker).
- Persistent bleeding after an amenorrheic period, especially if the bleeding is associated with pain.
- "Normal" symptoms of pregnancy, but with bleeding and dizziness.
- Pain in the tip of the shoulder (because blood enters the abdomen and causes irritation of the diaphragm).

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[1]Centre for Maternal and Child Enquiries (CMACE) (2011), BJOG 118 (Suppl. 1), 1-203.
[2] Westhoff C et al. Six-year contraceptive efficacy and continued safety of a levonorgestrel 52 mg intrauterine system. Contraception, 2020; 101: 159–161.
[3] Torpy JM, Burke AE, Golub RM. JAMA patient page. Ectopic pregnancy. JAMA 2012;308:829.
[4] Patient.co.uk. Ectopic Pregnancy. 2012. Available at http://www.patient.co.uk/health/Ectopic-Pregnancy.htm (accessed 23 November 12 A.D.).
[5] NHS Choices. Symptoms of ectopic pregnancy. 2012. Available at http://www.nhs.uk/Conditions/Ectopic-pregnancy/Pages/Symptoms.aspx (Last reviewed 27 November 2018).

- Severe pain or collapse due to severe internal bleeding combined with rupture.
- General symptoms: diarrhoea, feeling of weakness or pain during bowel movements; these symptoms only give cause for concern if they occur in addition to any of the specific symptoms listed above.
- A positive pregnancy test.

Early diagnosis of ectopic pregnancy can be difficult and may require a number of examinations. An ectopic pregnancy can be confirmed by a transvaginal ultrasound examination and a blood test for β-hCG.[6]

Influence of ectopic pregnancy on the patient's fertility

An ectopic pregnancy can result in damage to or loss of a reproductive organ (e.g. fallopian tube), which in turn can adversely affect a woman's future fertility. Since an ectopic pregnancy may impact future fertility, the benefits and risks of using LNG-IUS should be carefully evaluated for each patient.

Ectopic pregnancy and contraceptive counselling

Women should be informed about the benefits and risks of all available contraceptives, including LNG-IUS, so that they can make an informed decision. This includes advice on the individual risks of ectopic pregnancy in relation to the use of the LNG-IUS. Women who subsequently choose LNG-IUS should be educated on how to recognise the signs and symptoms of pregnancy, especially ectopic pregnancy, and that they should consult a physician immediately if any of these signs or symptoms occur. Women should also be informed that in the unlikely event that they become pregnant while using LNG-IUS, they must immediately consult a doctor to either rule out or confirm ectopic pregnancy.

Risk factors

The doctor should assess the individual risk of ectopic pregnancy on an individual basis for women considering using Gedeon Richter LNG-IUS as the contraceptive of choice. Risk factors for an ectopic pregnancy include:

- Previous ectopic pregnancy[7]
- Age (the risk increases with age)[7]
- Smoking (the risk increases with the number of cigarettes smoked)[7]
- Previous spontaneous abortion or induced abortion[7] (although no association was found in another study, see footnote † to Table 2)
- Previous sexually transmitted disease with inflammatory pelvic disease[7]
- Previous fallopian tube surgery[7]
- History of infertility[7]
- Multiple sexual partners[7]
- Endometriosis[3]

A case-control study was performed to assess risk factors associated with ectopic pregnancies based on data from the Auvergne ectopic pregnancy registry (France) and associated case-control

[6] Kazandi M & Turan V. Ectopic pregnancy; risk factors and comparison of intervention success rates in tubal ectopic pregnancy. Clin Exp Obstet Gynecol 2011;38:67– 70.

[7] Bouyer J, Coste J, Shojaei T et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol 2003;157:185–194.

studies.[7] A total of 803 cases of ectopic pregnancy and 1,683 births were included in the analysis, resulting in sufficient test power to fully investigate all risk factors for ectopic pregnancies. The statistically significant major risk factors for ectopic pregnancies using logistic regression analysis are presented in Table 2.

Table 2. Statistically significant risk factors for ectopic pregnancies according to the final logistic regression analysis (random effects model), Auvergne Register, France, 1993-2000

Variable	Adjusted OR	95% CI	*p*-value†
Age of woman (years)			
< 20	0.6	0.2, 2.1	
20–24	0.9	0.7, 1.3	
25–29	1		0.01
30–34	1.3	1.0, 1.7	
35–39	1.4	1.0, 2.0	
≥ 40	2.9	1.4, 6.1	
Smoking			
non-smoker	1		< 0.001
Past smoker	1.5	1.1, 2.2	
1-9 cigarettes/day	1.7	1.2, 2.4	
10-19 cigarettes/day	3.1	2.2, 4.3	
≥ 20 cigarettes/day	3.9	2.6, 5.9	
Prior spontaneous abortions			
None	1		0.02
1–2	1.2	0.9, 1.6	
≥ 3	3.0	1.3, 6.9	
Prior induced abortions			
None	1		0.05
surgical only	1.1	0.8, 1.6	
medical (or medical and surgical)	2.8	1.1, 7.2	
Prior sexually transmitted disease			
None	1		<0.001
Yes, without salpingitis.	1.0	0.8, 1.3	
Yes, with probable pelvic inflammatory disease‡	2.1	0.8, 5.4	
Yes, with confirmed pelvic inflammatory disease§	3.4	2.4, 5.0	
Prior tubal surgery			
No	1		< 0.001

Variable	Adjusted OR	95% CI	*p*-value†
Yes	4.0	2.6, 6.1	
Previous use of oral contraceptives			
No	1		0.03
Yes	0.7	0.5, 1.0	
History of infertility			
No	1		< 0.001
< 1 year	2.1	1.2, 3.6	
1-2 years	2.6	1.6, 4.2	
> 2 years	2.7	1.8, 4.2	

Note: Only the risk factors associated with a significant trend (*p-value*) for ectopic pregnancy in logistic regression are shown.

Note: Past ectopic pregnancy and multiple sexual partners were NOT included in the final logistic regression analysis. In a univariate analysis, however, the unadjusted OR was 12.5 for women with 1 prior ectopic pregnancy; 76.6 for women with ≥ 2 prior ectopic pregnancies (with $p < 0.001$ for trend); 1.6 for a total number of sexual partners > 5 and 1.0 for a total number of sexual partners of 2-5 ($p = 0.003$ for trend).

† Another case-control study found no significant association between prior spontaneous abortion and ectopic pregnancy.[8]

‡ Probable inflammatory pelvic disease associated with fever, abdominal pain and vaginal discharge.

§ Inflammatory pelvic disease confirmed by laparoscopy and/or positive serological tests for Chlamydia trachomatis

CI: confidence interval; OR: odds ratio

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the MHRA Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

It is also requested that suspected adverse reactions are reported to the marketing authorisation holder, Telephone: +44(0)207 604 8800. E-mail: drugsafety.uk@gedeonrichter.eu

[8] Barnhart KT, Sammel MD, Gracia CR et al. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril 2006;86:36–43.